JACC Vol. 30, No. 7
December 1997:1618–24

Prognostic Implications of Restrictive Left Ventricular Filling in Acute Myocardial Infarction: A Serial Doppler Echocardiographic Study

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Objectives. **This study was designed to evaluate the relative prognostic significance of restrictive left ventricular (LV) filling after acute myocardial infarction.**

Background. **Data regarding the contribution of diastolic dysfunction to prognosis after myocardial infarction are limited, and the additional value over the assessment of systolic dysfunction is not known.**

Methods. **Serial Doppler echocardiography was performed in 95 patients on days 1, 3 and 7 and 3 months after acute myocardial infarction. Patients were classified into two groups: a restrictive group (n = 12) with a peak velocity of early diastolic filling wave (E)/peak velocity of late filling wave (A) ratio ≥2 or between 1 and 2 and a deceleration time (DT) ≤140 ms during at least one echocardiographic study; and a nonrestrictive group (n = 83) with an E/A ratio ≤1 or between 1 and 2 and a DT >140 ms at all examinations.**

Results. **Cardiac death occurred in 10 patients during a mean follow-up interval of 32 ± 17 months. The survival rate at 1 year was 100% in the nonrestrictive group and only 50% in the restrictive group. After 1 year there was a continuing divergence of mortality, resulting in a 3-year survival rate of 100% and 22%, respectively. Univariate Cox analysis revealed that restrictive LV filling, wall motion score index, ejection fraction and end-systolic and end-diastolic volume indexes, as well as peak creatine kinase, peak MB fraction and heart failure during the hospital course were significant predictors of cardiac death, although restrictive filling was the single best predictor ($p < 0.0001$). Multivariate analysis showed that restrictive filling adds prognostic information to clinical and echocardiographic variables of systolic dysfunction.**

Conclusions. **Restrictive LV filling after acute myocardial infarction is the single best predictor of cardiac death and adds significantly to clinical and echocardiographic markers of systolic dysfunction.**

(J Am Coll Cardiol 1997;30:1618–24)

The extent of left ventricular (LV) systolic dysfunction and LV end-systolic volume are important predictors of survival after acute myocardial infarction (1–3). However, the contribution of LV diastolic dysfunction to long-term prognosis has not been well defined. Pulsed Doppler echocardiography has proved useful in the assessment of LV diastolic filling (4–8). Three distinct patterns have been described and correlated with hemodynamic and clinical features in various cardiac disease states (4–7,9–12). The restrictive filling pattern, characterized by a short deceleration time (DT) of early diastolic filling wave and an increased ratio of peak velocity of early diastolic filling wave (E) to peak velocity of late filling wave (A) (E/A ratio), has been associated with high left ventricular filling pressures and advanced New York Heart Association functional class (9–15). In patients with severe LV dysfunction (13,16), congestive heart failure (17), dilated cardiomyopathy (14,15,18,19) and cardiac amyloidosis (20), this pattern has been found to be predictive of cardiac death. Little information is available about diastolic filling and long-term outcome after myocardial infarction (21), and it is unclear whether Doppler variables can provide independent prognostic information over that of the assessment of LV systolic function. The primary objective of this study was therefore to determine the prognostic significance of the restrictive filling pattern after acute myocardial infarction and to evaluate whether this variable could add significantly to markers of LV systolic dysfunction. The second objective was to examine the clinical and echocardiographic characteristics of patients with restrictive LV filling.

Methods

Patients. The study group consisted of 95 consecutive hospital survivors of acute myocardial infarction, diagnosed by a history of typical chest pain, ST segment elevation in two contiguous leads and a transient rise in creatine kinase exceeding twice the upper limit of normal. Patients were excluded if

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Manuscript received February 17, 1997; revised manuscript received August 1, 1997, accepted August 21, 1997.

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0735-1097/97/$17.00
PII S0735-1097(97)00369-0

Abbreviations and Acronyms

A = peak velocity of late diastolic filling wave
DT = deceleration time
E = peak velocity of early diastolic filling wave
LV = left ventricle (ventricular)

they had prior Q wave myocardial infarction. Other exclusion criteria were atrial fibrillation (n = 2), moderate to severe mitral regurgitation according to the method of Helmcke et al. (22) (n = 4), severe aortic stenosis (n = 1) and technically inadequate Doppler echocardiographic studies for quantitative analysis (n = 7). All patients gave informed consent to participate in this prospective study, which had been approved by the Science and Ethics Committee of our institution.

Two-dimensional and Doppler echocardiography. Serial two-dimensional and Doppler echocardiography was performed with a Hewlett-Packard Sonos 1000 or Sonos 1500 with use of a 2.5-MHz transducer. The examinations were performed within 24 h of admission and repeated on the 3rd and 7th days and 3 months after the acute event. All two-dimensional echocardiographic studies included standard parasternal and apical views and were stored on 0.5-in. VHS videotape for subsequent analysis. Regional wall motion was assessed semiquantitatively by two experienced observers using a 13-segment division of the LV (23). Wall motion for each segment was graded visually as 1 = normokinesia, 2 = hypokinesia, 3 = akinesia and 4 = dyskinesia. Wall motion score index was calculated by summing the scores for each segment and dividing by the number of segments analyzed. LV end-diastolic and end-systolic volumes were determined from apical two- and four-chamber views by using the Simpson biplane formula according to the recommendations of the American Society of Echocardiography (24). Tracing of the endocardial borders was performed on a digitized frame from the technically best cardiac cycle (Image Vue, Nova Microsonics), and volumes were normalized for body surface area. Ejection fraction was calculated as (End-diastolic − End-systolic volume)/End-diastolic volume.

Pulsed Doppler mitral flow velocity was obtained by placing the sample volume between the tips of the mitral leaflets in the apical four-chamber view. In each patient, measurements from five cardiac cycles were obtained and averaged. The following variables were measured: E; A; E/A ratio and DT of early filling. Patients were assigned to one of two groups based on Doppler measurements of LV filling: a restrictive group (12 patients) with an E/A ratio ≥2 or E/A between 1 and 2 and DT ≤140 ms during at least one echocardiographic study, and a nonrestrictive group (83 patients) with an E/A ratio ≤1 or E/A between 1 and 2 and DT >140 ms during all echocardiographic examinations (16,17).

Statistical analysis. Baseline descriptive data are presented as mean value ± SD. Comparisons between groups for continuous data were made with an unpaired Student *t* test. Differences between proportions were assessed by chi-square analysis. Cardiac mortality was compared between subgroups by using the Mantel-Cox log-rank test, and cardiac survival curves were computed with the Kaplan-Meier method. Clinical, echocardiographic and Doppler variables were compared for their ability to predict cardiac mortality by means of the Cox proportional hazards model. Variables that were significantly different between survivors and nonsurvivors by unpaired *t* testing or by chi-square testing were included in the Cox model. Clinical variables selected for multivariate analysis were LV heart failure during the hospital stay and enzymatic infarct size. The diagnosis of LV heart failure was based on the presence of at least two of the following criteria: bibasilar pulmonary rales, dyspnea, a third heart sound or radiographic evidence of pulmonary congestion (2). Echocardiographic variables included LV volume indexes, ejection fraction and wall motion score index. The Doppler variable selected was presence of restrictive filling. The statistical package for Biomedica Computer Program (BMDP Statistical Software Inc.) software was used. A p value < 0.05 was considered significant.

Results

Patient characteristics. Restrictive LV filling was found in 12 (13%) of 95 patients. In 10 of these patients the restrictive pattern was observed within the 1st week after myocardial infarction. The incidence was highest (75%) on the 7th day, compared with 42% and 58% on the 1st and the 3rd day, respectively. After 3 months, LV filling changed toward "normal" in five patients. However, four patients had persistent restrictive filling, whereas two others showed this pattern for the first time. Clinical and echocardiographic characteristics of patients with and without restrictive filling are summarized in Table 1. Patients with restrictive filling had a significantly larger enzymatic infarct size and more often showed signs or symptoms of LV heart failure during the hospital course. In addition, they had significantly larger LV end-diastolic and end-systolic volume indexes, lower ejection fraction and higher wall motion score index than patients without restrictive filling. More specifically, restrictive LV filling was found only in patients with an ejection fraction <45% and a wall motion score index ≥1.76.

The incidence of reinfarction during the follow-up period was similar in patients with and without restrictive filling (8% and 4%, respectively). Hospital admission for heart failure had occurred in three patients with restrictive filling (25%) compared with two patients without restrictive filling (2.4%, $p < 0.005$). Furthermore, additional revascularization procedures were performed in 20 (24%) of the 83 patients without restrictive filling but in none (0%) of the 12 patients with restrictive filling (p = NS).

Outcome. Patients were followed up for 32 ± 17 months (range 1 to 69). During this period 10 patients (11%) died of cardiac causes (6 patients from sudden death, 4 from progressive congestive heart failure) and 3 patients (3%) died of noncardiac causes. Cardiac death occurred in all four patients

Table 1. Baseline Characteristics of the Study Patients

	Nonrestrictive Group (n = 83)	Restrictive Group (n = 12)	p Value
Age (yr)	61 ± 11	62 ± 8	NS
Male	63 (76%)	11 (92%)	NS
Anterior myocardial infarction	51 (61%)	9 (75%)	NS
Inferior myocardial infarction	32 (39%)	3 (25%)	NS
Thrombolytic therapy	67 (81%)	8 (67%)	NS
Primary PTCA	6 (7%)	1 (8%)	NS
Q wave infarction	64 (77%)	12 (100%)	NS
Peak creatine kinase (U/liter)	1,382 ± 898	2,584 ± 1,078	< 0.0005
Peak MB fraction (U/liter)	127 ± 92	222 ± 85	< 0.005
Heart failure*	11 (13%)	7 (58%)	< 0.001
Medication at hospital discharge			
Beta-blockers	62 (75%)	9 (75%)	NS
ACE inhibitors	39 (47%)	8 (67%)	NS
Nitrates	11 (13%)	3 (25%)	NS
Calcium channel antagonists	2 (2%)	1 (8%)	NS
End-diastolic volume index (ml/m^2)	63 ± 9	70 ± 6	< 0.01
End-systolic volume index (ml/m^2)	32 ± 8	42 ± 6	< 0.0001
Ejection fraction (%)	50 ± 7	40 ± 5	< 0.0001
Wall motion score index	1.56 ± 0.22	1.83 ± 0.14	< 0.0005

*During hospital stay. Data are presented as mean value ± SD or number (%) of patient group. ACE = angiotensin-converting enzyme; PTCA = percutaneous transluminal coronary angioplasty.

with persistent restrictive filling, in three of the five with reversible restrictive filling and in one of the two with late onset restrictive filling. One patient with a restrictive pattern during the hospital stay, died before the 3-month examination. Figure 1 shows the actuarial survival curves for cardiac death of patients with and without restrictive filling. The survival rate at 1 year was 100% in the non-restrictive group and 50% in the restrictive group. After 1 year there was a continuing divergence of mortality, resulting in a 3-year survival rate of 100% and 22%, respectively. Figure 2 shows survival curves for cardiac death, constructed by classifying the patients into two groups based on indexes of systolic dysfunction. Although stratification by wall motion score index, ejection fraction or end-systolic volume index provided a clear separation of survival curves and a highly significant prediction of mortality (log-rank chi-square = 17.6, $p < 0.0001$; log-rank chi-square = 22.4, $p < 0.0001$; and log-rank chi-square = 12.3, $p = 0.0005$, respectively), stratification by Doppler transmitral filling pattern provided a wider separation of survival curves and a higher prediction of cardiac death (log-rank chi-square = 76.1, $p < 0.0001$).

Cox proportional hazards model analysis. At univariate analysis, enzymatic infarct size, heart failure during hospital stay, LV volumes, ejection fraction, wall motion score index

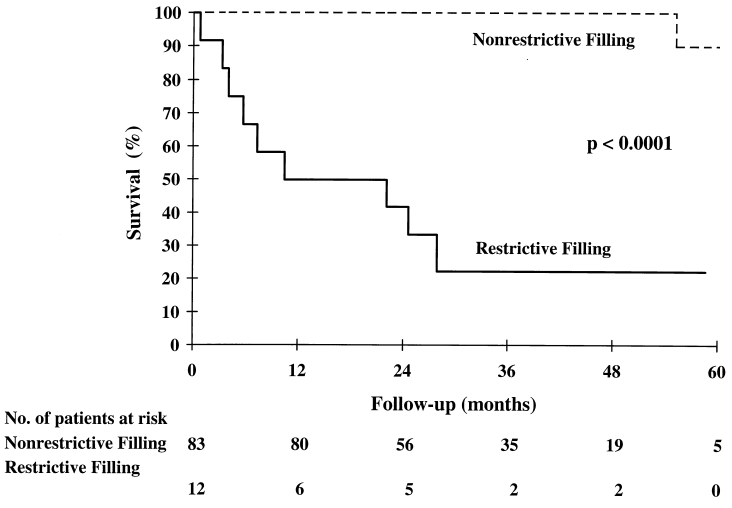

Figure 1. Effect of Doppler-derived LV filling on cardiac survival. Note the wide divergence of both curves, with cardiac survival rates of 50% versus 100% at 1 year and 22% versus 100% at 3 years, in patients with restrictive and nonrestrictive filling, respectively.

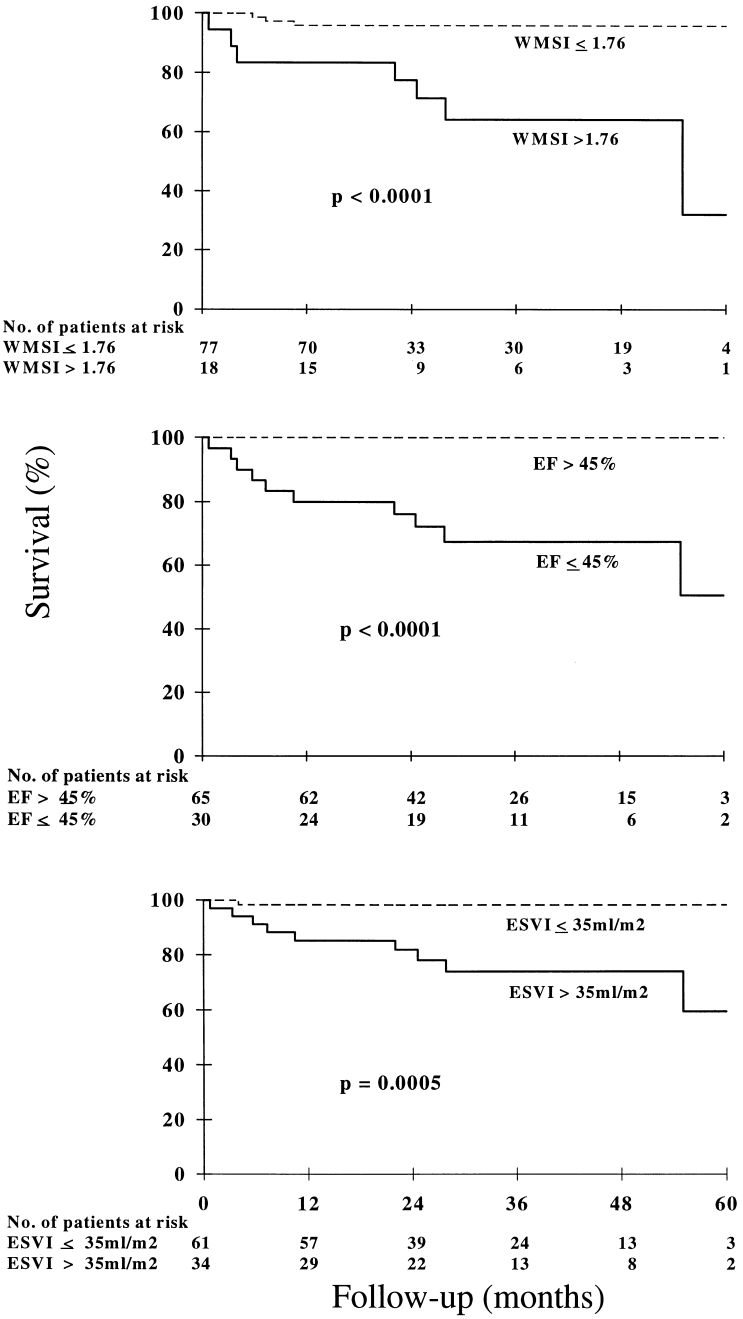

Figure 2. Cardiac survival curves according to wall motion score index (WMSI, **top**), ejection fraction (EF, **middle**) and end-systolic volume index (ESVI, **bottom**). All methods of classification provide a clear separation of survival curves and a significant prediction of cardiac death; however, the separation of survival curves is smaller than that depicted in Figure 1.

and restrictive filling were all predictive of cardiac death. Table 2 shows these variables and their relative risks in decreasing order of power. Restrictive LV filling was the single best predictor ($p < 0.0001$). When this analysis was performed in the subgroup of 30 patients with an ejection fraction <45%, restrictive filling was the only variable predictive of cardiac death ($p < 0.005$). Multivariate Cox analysis was performed to assess the additional prognostic value of restrictive filling (Table 3). Three different models were used; model 1 includes only the significant clinical variables. Addition of echocardiographic data reflecting systolic dysfunction (model 2) improved the global chi-square (an index of the predictive power) from 21.9 to 26.0. Addition of restrictive filling (model 3) further improved this value to 77.1. The best two-variable combination for prediction of cardiac death was that of restrictive filling and heart failure during the hospital stay, with a global chi-square of 76.7.

Multivariate Cox analysis was also performed for all-cause mortality and occurrence of heart failure. Restrictive filling was the only independent predictor of all-cause mortality, whereas restrictive filling and ejection fraction were both independent predictors for occurrence of heart failure.

Table 2. Univariate Cox Model Rankings of Doppler Echocardiographic and Clinical Variables Predicting Cardiac Death

	Wald Chi-Square	p Value	Relative Risk (95% CI)
Restrictive filling	18.13	0.0000	90.2 (11–716)
Ejection fraction (%)	13.84	0.0002	4.7 (1.2–19)*
End-systolic volume index (ml/m^2)	11.79	0.0006	15.7 (2.0–123)*
Wall motion score index	11.67	0.0006	10.3 (2.7–40)*
Peak creatine kinase (U/liter)	10.33	0.0013	8.7 (1.8–41)*
Heart failure during hospital course	9.61	0.0019	7.4 (2.1–26)
Peak MB fraction (U/liter)	8.99	0.0027	13.0 (1.7–103)*
End-diastolic volume index (ml/m^2)	4.69	0.0303	5.1 (1.1–24)*

*Relative risks were calculated for ejection fraction ≤40%, end-systolic volume index >35 ml/m^2, wall motion score index >1.76, peak creatine kinase >2,000 U/liter, peak MB fraction >150 U/liter and end-diastolic volume index >65 ml/m^2. CI = confidence interval.

Discussion

Doppler echocardiography and diastolic dysfunction. It has been shown (4–8) that, despite some limitations, pulsed Doppler echocardiography provides a useful noninvasive tool for assessment of LV diastolic properties. In fact, three abnormal patterns have been described and correlated with hemodynamic findings (4). One pattern, characterized by reduced early filling, increased or normal atrial filling (decreased E/A ratio) and prolonged DT of early filling, is thought to be the consequence of impaired relaxation in the presence of normal LV filling pressures. It has been described in normal aging, ventricular hypertrophy, systemic hypertension and acute ischemia (4,6,7,25–29). The opposite pattern, referred to as restrictive, is characterized by increased early filling, reduced atrial filling (increased E/A ratio) and short DT of early filling. It is associated with high LV filling pressures and increased chamber stiffness and is observed in advanced cardiac disease of various origins (5). The short DT suggest an early equalization of pressures in the left atrium and LV. The third pattern is essentially a normal pattern that has been termed "pseudonormal." This pattern may represent a transitional state between impaired relaxation and restrictive patterns in patients with LV systolic dysfunction.

Table 3. Multivariate Cox Model Analysis

Model	Variables	Global Chi-Square	p Value
1	Only clinical variables: heart failure, enzymatic infarct size	21.9	0.0001
2	Addition of echocardiographic variables: wall motion score index, ejection fraction, end-systolic and end-diastolic volume indexes	26.0	0.0005
3	Addition of Doppler variable: restrictive filling pattern	77.1	0.0000

LV filling and myocardial infarction. To date, several investigators have studied LV filling in patients with myocardial infarction (10,11,30–34). All aforementioned distinct patterns have been described. An abnormal relaxation pattern has been shown to be more common in patients with a small infarction (32,34). In contrast, patients with a large infarction often exhibit a "pseudonormalized" or even a restrictive pattern within the 1st week. It has been demonstrated that this pattern frequently changes over time into a less restrictive pattern, maybe as result of LV remodeling (32,34). In agreement with those previous observations, our study showed that patients with restrictive LV filling had an enzymatically large infarction. Furthermore, all patients had moderate to severe LV systolic dysfunction manifested by low ejection fraction, high wall motion score index and increased LV volume indexes. Also, LV heart failure was frequently observed during the hospital course. In line with previous studies (32,34), serial measurements in the present study revealed that the restrictive pattern occurred most frequently on the 7th day after myocardial infarction and "normalized" in 50% of the patients 3 months later. There was a trend toward higher cardiac mortality rate in patients with persistent restrictive filling than in those with reversible or late onset restrictive filling, although the small number of patients in our study limited the detection of differences. Preliminary studies performed in patients with dilated cardiomyopathy (35) or congestive heart failure (36) showed that reversibility of restrictive filling is associated with better outcome. Future large scale serial Doppler echocardiographic studies are needed to assess the effect of timing and reversibility of restrictive filling after myocardial infarction and to evaluate whether more aggressive treatment (e.g., early revascularization procedures) may provide a more favorable prognosis in these patients.

Prognostic implications of restrictive filling. Recently, several studies (13–20) have shown that Doppler-derived diastolic filling variables—in particular, E/A ratio >2 and short DT of early filling—are important predictors of cardiac death in patients with various cardiac diseases. In both symptomatic and asymptomatic patients with advanced LV systolic dysfunction of various origins, restrictive filling provides important prognostic information and may be valuable in identification of a high risk subgroup. However, data are limited on patients with myocardial infarction (21). Pozzoli et al. (21) showed that a predominantly early diastolic filling pattern (E/A ratio >1) 3 to 12 weeks after myocardial infarction in patients with an ejection fraction <40% was associated with adverse outcome. The present study demonstrates that restrictive LV filling is the single best predictor of cardiac death. It adds significant prognostic information to indicators of systolic dysfunction (ejection fraction and end-systolic volume), which are currently recognized as the most important indicators of poor outcome after myocardial infarction. Thus, restrictive filling identifies a subgroup of patients at very high risk of cardiac death within the group of patients with moderate to severe systolic dysfunction. An explanation for this observation may be the markedly elevated filling pressure often found in those

patients (10,11). Both Pozzoli et al. (10) and Giannuzzi et al. (11) have shown a strong relation between restrictive filling and elevated pulmonary wedge pressure in postinfarction patients with LV systolic dysfunction. An E/A ratio >2 was associated with a pulmonary capillary wedge pressure ≥20 mm Hg in 96% of patients, whereas E DT provides an accurate estimate of LV filling pressure in patients with a normal E/A ratio (11). The long-term prognostic importance of elevated pulmonary wedge pressure after myocardial infarction has been demonstrated in previous studies (37–39).

Study limitations. Doppler-derived LV filling could be influenced by multiple factors, including age, heart rate, loading conditions and left-sided valvular disease. In our study, age was not different between patients with and without restrictive filling, and we excluded patients with moderate to severe mitral regurgitation or aortic stenosis. Heart rate, blood pressure and medical treatment were not characterized in this study. At the first echocardiographic examination (within 24 h), heart rate was higher in patients with restrictive filling, whereas blood pressure was not significantly different. However, an increased heart rate has been demonstrated to increase atrial filling, resulting in a nonrestrictive rather than restrictive pattern (40). Furthermore, medical treatment at discharge was not different between the two patient groups and therefore would be unlikely to affect our results. Another limitation of the present study is the relatively small patient group. Specifically the number of patients with restrictive filling or cardiac death may be too small to detect differences between groups as a result of insufficient power. This may especially be true for differences in additional revasularization procedures, which could influence survival.

Conclusions and clinical implications. The present study demonstrates that Doppler-derived LV filling, specifically the restrictive filling pattern, is a powerful independent predictor of cardiac death in patients with acute myocardial infarction. It adds significant prognostic information to indicators of systolic dysfunction and allows further identification of a subgroup at very high risk for cardiac death among those with a large infarction. Because the restrictive pattern was observed most frequently on the 7th day after myocardial infarction and occurred only in patients with an ejection fraction <45%, we recommend (repeat) Doppler echocardiography before discharge in this subset of patients. Whether outcome in patients with restrictive filling may be improved by an aggressive therapeutic approach should be evaluated in future studies.

We gratefully acknowledge the statistical advice of Piet G.M. Jansen, MD, PhD.

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